Autologous anti-CD19-transduced CD3+ cells (relapsed or refractory mantle cell lymphoma); Requirement of Routine Practice Data Collection and Evaluations

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Requirement of routine practice data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGBV for the active ingredient autologous anti-CD19-transduced CD3+ cells in the treatment of:

Adults with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

1. Requirements for routine practice data collection and evaluations

With reference to the justification for the requirement of routine practice data collection for the active ingredient autologous anti-CD19-transduced CD3+ cells (hereinafter referred to as brexucabtagene autoleucel) for the purpose of the benefit assessment, which forms the basis of the procedure-initiating resolution on the requirement of routine practice data collection of 7 October 2021, the following requirements arise:

1.1 Question according to PICO scheme

Population	Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after 2 or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor[a]
Intervention	▪ Autologous anti-CD19-transduced CD3+ cells (brexucabtagene autoleucel) The marketing authorisation and the dosage information in the product information for brexucabtagene autoleucel (Tecartus®) must be taken into account.
Comparator	Patient-individual therapy with selection of: – Bendamustine + rituximab – Bortezomib ± rituximab – Lenalidomide ± rituximab – R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) – VRCAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone) – Ibrutinib – R-BAC (rituximab + bendamustine + cytarabine)

	– Temsirolimus – R-FCM (fludarabine + cyclophosphamide + mitoxantrone + rituximab) – R-Cb (rituximab + chlorambucil) – Venetoclax – High-dose therapy with allogeneic stem cell transplantation – High-dose therapy with autologous stem cell transplantation taking into account the response and duration of remission of previous therapies and the general condition.
Outcome	Mortality ▪ Overall survival Morbidity ▪ Symptomatology Health-related quality of life Side effects ▪ Serious adverse events (operationalised as events leading to hospitalisation or prolonging an existing hospitalisation and events leading to death; overall rate) ▪ adverse events leading to hospitalisation or prolonging an existing hospitalisation (overall rate) a) Specific adverse events (with information on the respective severity grade including specific adverse events leading to a significant impairment of the activity of daily living or with CTCAE grade ≥ 3): - Cytokine Release Syndrome (CRS) - Neurologic events (including immune effector cell-associated neurotoxicity syndrome, encephalopathy and peripheral neuropathy) - Infections - Cytopenias (anaemia, leukopenia, thrombocytopenia) - Hypogammaglobulinemia - Tumour Lysis Syndrome (TLS) - Graft-versus-Host Disease (GvHD) - Secondary neoplasms - Cardiac arrhythmias - Heart failure (new onset))

a	The criteria for the suitability of treatment with brexucabtagene autoleucel are to be applied to the inclusion and exclusion criteria for routine practice data collection and evaluations.

1.2 Type and methods of data collection

Taking into account the question of the routine practice data collection and the methodological limitations of non-randomised comparisons, the following requirements are placed on the study design and the data source for the present routine practice data collection.

1.2.1 Requirements for the study design

- Non-randomised, prospective comparison of brexucabtagene autoleucel with the listed comparator preferably as a comparative registry study or, if a comparative registry study is not feasible, as a comparative study using a data platform to be set up specifically for the present routine practice data collection (study-specific data collection).
- For the enrolment in the study and the start of observation of the patients, the time of the treatment decision should be chosen based on an intention-to-treat principle

1.2.2 Data source requirement

- Use of registries or a data platform to be set up specifically for the present routine practice data collection as a data source, which meet the requirements of routine practice data collection and fulfil at least the following quality criteria[1]:
  - Detailed registry description or description of the data platform (protocol)
  - Exact definition or operationalisation of exposures (type and duration of medicinal therapy and other concomitant therapies), clinical events, endpoints and confounders
  - Use of standard classifications and terminologies
  - Use of validated standard data collection tools (questionnaires, scales, tests)
  - Training courses on data collection and recording
  - Implementation of a consensus disease-specific core data set
  - Use of exact dates for the patient, the disease, important examinations and treatments/ interventions
  - Clearly defined inclusion and exclusion criteria for patients
  - Strategies to avoid selection bias in patient inclusion to achieve representativeness

[1] IQWiG Rapid Report A21-130: Concept for routine practice data collection – brexucabtagene autoleucel.

- Specifications to ensure completeness of data per data collection time point and completeness of data collection time points
- Source data verification for 100% of patients per data collection site for the primary endpoint and for at least 10% of randomly selected patients per data collection site for all other endpoints over the period since the start of data collection
- When using a registry: Ensuring scientific independence and transparency

- Use of a registry or a data platform to be set up specifically for the present routine practice data collection, in which treatment of relapsed or refractory mantle cell lymphoma is carried out in accordance with German daily care or is sufficiently similar to care in Germany

1.2.3 Primary data source and integration of further data sources

For the study design in the form of a comparative registry study, the following specifications must be taken into account:

- Use of the European indication-specific registry EMCL as primary registry; provided that the quality criteria mentioned in section 1.2.2 are fulfilled

An integration of further data sources (especially registries) is also possible, taking into account all the data source requirements mentioned in section 1.2.2.

1.3 Duration and scope of data collection

Taking into account that the patients in the present therapeutic indication are in an advanced stage of the disease, in which the main therapeutic goal is an extension of overall survival, as well as the possible plateauing of overall survival observed in the pivotal phase II ZUMA-2 study, the following duration of observation should be implemented during routine practice data collection:

- Follow-up of patients for at least 36 months

As an approximation of the appropriate sample size for routine practice data collection, the following sample size is assumed as a result of an orienting sample size estimate, based on the endpoint of mortality:

- 190 patients (orienting sample size estimate) assuming an equal distribution between intervention and comparison group; if the recruitment possibilities for the comparator group are limited, the sample size estimate can also be based on the assumption of a different distribution between the intervention and the comparator group (for example 2:1).

1.4 Evaluations of the data for the purpose of the benefit assessment

The pharmaceutical company shall submit the following evaluations to the G-BA:

- Interim analyses

  Evaluations of 3 interim analyses shall be presented. The relevant times for the performance of the interim analyses shall be the times specified in section 2.3.

  The interim analyses shall be performed according to the specifications in the study protocol and statistical analysis plan (see section 1.5). In the process, a check for discontinuation due to futility must also be carried out for each interim analysis.

  On the 1st Interim analysis:

  Based on this interim analysis, a final sample size estimate will be made using the more precise effect assumptions rendered possible. The endpoint of overall survival should be used and the shifted hypothesis boundary should be taken into account in accordance with the procedure in IQWiG's[1] concept.

The interim analyses shall be prepared on the basis of module 4 of the dossier template, providing the full texts and study documents.

- Final evaluations for the purpose of the renewed benefit assessment

  The final evaluations shall be carried out according to the specifications in the study protocol and statistical analysis plan. For the transmission of the final evaluations to the G-BA, the time specified in section 3 applies.

The final evaluations shall be prepared in a dossier in accordance with the provisions of Section 9 paragraphs 1 to 7 of the Rules of Procedure of the G-BA.

1.5 Requirements for the preparation of the study protocol and statistical analysis plan

The pharmaceutical company shall prepare a study protocol and a statistical analysis plan before carrying out routine practice data collection and evaluations.

When preparing the study protocol and statistical analysis plan, the pharmaceutical company shall address the necessary adaptations to the identified indication-specific registry. With regard to the implementation of the collection of patient-reported endpoints on symptomatology and health-related quality of life, for the approval of the study documents, it must be confirmed:

- whether an adaptation of the identified indication-specific registry to the present requirements for the recording of patient-reported symptomatology and health-related quality of life is possible and within what period of time this can be realised, as well as any effects of the necessary adaptation period on the recruitment possibilities for the prospective comparator group

With regard to the evaluation of the data, the following information in particular must be presented in advance in the study protocol and statistical analysis plan:

- Information on the statistical methods and models used, as well as naming the procedures and the criteria used in model selection and adaptation
- Information on the expected scope and reasons for missing data, as well as measures to avoid missing data and evaluation strategies to deal with missing data
- Information on dealing with implausible data and outliers
- Information on planned sensitivity analyses
- Information on the start of observation of the patients
- Information on the operationalisation of the criteria for the suitability of treatment with brexucabtagene autoleucel
- Information on the identification, as well as the adequate, pre-specified adjustment for confounders
- Information on the investigation of potential effect modifiers
- Information on interim analyses taking into account the requirements under section 1.4 and the specifications under section 2.3
- Information on discontinuation criteria due to futility

2. Requirements for checking whether the pharmaceutical company has fulfilled its obligation to carry out routine practice data collection and evaluations

2.1 Submission of a study protocol as well as the statistical analysis plan for coordination with the G-BA

The final drafts for a study protocol and for a statistical analysis plan prepared by the pharmaceutical company are to be submitted to the G-BA for approval by 21 December 2022 at the latest.

The G-BA, with the involvement of IQWiG, carries out a review of the study protocol and the statistical analysis plan and usually communicates the result to the pharmaceutical company in writing within 12 weeks.

Before submitting the requested documents to the G-BA, the pharmaceutical company has the option to request a consultation with the G-BA according to Section 35a, paragraph 7 SGB V in conjunction with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). The subject of such consultation is, in particular, the drafts for a study protocol as well as for a statistical analysis plan. In order to enable the pharmaceutical company to adequately consider the aspects addressed in the consultation when preparing the study protocol and statistical analysis plan, the request for consultation must be submitted to the G-BA by 19 August 2022 at the latest.

If the Federal Joint Committee determines during the first submission of the study protocol and statistical analysis plan that the requirements of routine practice data collection and evaluations are insufficiently implemented, the pharmaceutical company is given the

opportunity to revise the study documents once. The Federal Joint Committee shall adopt a declaratory resolution in this regard in the procedure for routine practice data collection and evaluations, which shall set out the necessary need for adaptation of the study documents. The deadline for submission of the revised statistical analysis plan and study protocol is 4 weeks, unless otherwise specified in the declaratory resolution.

2.2 Submission of information on the course of data collection (in particular information on the status of recruitment)

6 months, 18 months, 36 months and 54 months after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution, the pharmaceutical company shall provide the G-BA in particular with the information on

- the number and the respective medicinal treatment of the patients included so far,
- patient-related observation periods, and
- any deviations regarding the expected number of recruits

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The G-BA may confirm the submitted statistical analysis plan and the study protocol by means of a declaratory resolution subject to the condition that further adaptations to the study documents deemed mandatory for the implementation of the requirements from this resolution must be made. In this case, the final study documents shall be submitted to the G-BA together with the submission of information on the course of data collection 6 months after the date of the start of routine practice data collection, which is to be defined by means of a declaratory resolution.

2.3 Submission of interim analyses

Interim analyses are to be carried out and corresponding evaluations submitted to the Federal Joint Committee at the following points in time after the time of the start of routine practice data collection, which is to be defined by means of a declaratory resolution, taking into account the requirements specified in section 1.4:

- 18 months after the start of routine practice data collection
- 36 months after the start of routine practice data collection
- 54 months after the start of routine practice data collection

3. Deadline for the submission of evaluations of the data collected as part of the routine practice data collection

For the performance of a new benefit assessment, the evaluations of data collected as part of the routine practice data collection must be submitted by 21 July 2028 at the latest.

The submission of these evaluations must be made in the form of a dossier in accordance with the provisions of Chapter 5, Section 9, paragraphs 1 to 7 of the Rules of Procedure of the G-BA, taking into account the requirements of this resolution in accordance with Chapter 5, Section 58 of the Rules of Procedure of the G-BA.